cases.[3] Mood disorders are said to occur in 24% of cases, with the vast majority of these patients suffering from major depression.[4] CADASIL presents with mood disturbance in up to 9% of cases,[5] usually depression,[6] but sometimes also bipolar disorder.[7] The cause of the mood disturbance is not clear. MRI studies in unipolar patients have failed to demonstrate an increased volume of abnormal white matter signal,[8] and linkage analysis has failed to support notch 3 as a candidate gene for bipolar disorder.[9] Headache occurs in 40% of CADASIL patients and usually takes the form of migraine with aura.[5] This case is unique in that acute severe "thunderclap" headache has not previously been described in CADASIL and led initially to investigations aimed at excluding the presence of subarachnoid haemorrhage. However, it is possible that the headache and the genetic disorder are coincidental in this case.

Other features of CADASIL include recurrent lacunar strokes which result in progressive disability, and cognitive decline with supervening sub-cortical dementia in the majority of patients.[5] No specific form of disease-modifying therapy has been found to be effective in CADASIL, and treatment is therefore symptomatic. However, correct diagnosis allows for crucial genetic counselling to be put in place for affected families. Among patients with recurrent headache there is a specific association between depression and migraine with aura.[10] Therefore, the probability that these common disorders co-exist is much greater than the probability that depression and migraine with aura are manifestations of underlying CADASIL.

However, this case illustrates that MRI may be an appropriate investigation in selected patients with depressive episodes if there is a strong personal or family history of migraine with aura, stroke, or cognitive impairment.[11] When abnormal signal is seen in the regions of the anterior temporal poles or external capsule-insula, skin biopsy may be considered. Skin biopsy is a rapid and highly specific method of diagnosis[12] but suffers from low sensitivity; a negative skin biopsy in the context of a high index of suspicion should thus prompt genetic testing for this disorder.

Declaration of Interest: None.

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Case report

Risperidone induced periorbital oedema

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Abstract

Antipsychotic medications are associated with adverse cutaneous reactions (ACRs) in approximately 2-3% of patients.[1] We present three cases of possible risperidone induced periorbital oedema in the absence of any other systemic or local cause responsible for the oedema. The development of periorbital oedema after the initiation of risperidone therapy, and disappearance after the discontinuation of this drug, suggests a possible causal relationship between periorbital oedema and risperidone. To our knowledge, there are very few reports of risperidone therapy and development of periorbital oedema. Risperidone is a valid and effective choice amongst antipsychotic medications, but these cases call for caution regarding ACRs at the time of prescribing.

Key words: Risperidone; Schizophrenia; Periorbital oedema.

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Case studies

Case 1

A 30 year old female admitted to our hospital for the management of undifferentiated schizophrenia of seven years duration, characterised by delusion of persecution, thought

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broadcasting and auditory hallucinations (third person), was started on oral risperidone 4mg/day. The patient developed an acute bilateral periorbital swelling within three days, although she did not complain about it. A possibility of periorbital swelling due to risperidone was considered, the drug was stopped immediately and the oedema subsided completely in three to four days. The patient was subsequently started on another atypical neuroleptic, olanzapine 10mg/day. The periorbital oedema did not recur again.

Case 2

A 26 year old female was diagnosed as paranoid schizophrenia of four years duration, characterised by delusion of persecution, delusion of reference and auditory hallucinations (running commentary type), was started on risperidone 4mg/day and was advised to follow up on outpatient basis. Within two days of starting risperidone, the patient reported to OPD with bilateral periorbital oedema. The dose of risperidone was halved and the oedema began to subside but her mental status deteriorated after decreasing the dose of risperidone. The dose of risperidone was again increased to 4mg/day and within three days the oedema also started worsening. Risperidone was discontinued and the oedema subsided completely over the next few days. The patient was then started on haloperidol 10mg/day, however, the oedema did not appear again.

Case 3

A 27 years old female, diagnosed as undifferentiated schizophrenia, was on follow up treatment from the outpatient department of our hospital. She was on haloperidol 15mg/day. But as she developed extrapyramidal symptoms while on haloperidol, the drug was changed to risperidone 4mg/day. Within two days of changeover of drugs, the patient developed bilateral periorbital oedema. The pharmacotherapy was stopped immediately and the oedema subsided in two days. The patient is being maintained well to date on haloperidol 10mg/day and trihexyphenidyl 4mg/day.

Discussion

In all the above cases, the patients were female. Past history of the first case was not known. There was no history of previous treatment with risperidone or any exposure to any contrast agent in the other two cases. On general physical examination the patients were afebrile, had appropriate weight for height and had no pallor. The vitals in all three cases were monitored regularly and were found to remain stable. There was no evidence of urticaria, oedema at any other site or any hoarseness of voice, dyspnoea or tachypnoea, stridor, or bronchospasm on examination of the respiratory system. The skin overlying the oedema was normal and there was no conjunctival involvement. The oedema was of pitting type, non tender and there was no diurnal variation.

Relevant laboratory investigations like complete blood count, erythrocyte sedimentation rate, liver, renal and thyroid function, and urinalysis were carried out and no abnormality was found in any of the three cases. Chest and skull x-ray were done and were found to be normal. Ophthalmology and dental referral were sought in all cases and no specific local cause could be found for the periorbital oedema.

The possible causes of oedema could be venous disorders, inflammatory disorders, certain systemic disorders, trauma, allergy, or malnutrition. Some drugs are known to cause periorbital oedema, eg. aspirin,[2] ibuprofen,[3] ziprasidone,[4] clozapine,[5] penicillin, and sulfa preparations. Histamine was thought to be the central factor in aspirin and ibuprofen induced oedema,[2,3] as it did not recur in the patients when they were pretreated with terfenadine.

Periorbital oedema is not one of the known adverse effects of risperidone. However, our patients clearly had risperidone induced oedema as no other medical cause could explain the oedema and it subsided almost immediately in all three cases with discontinuation of risperidone. Moreover, the problem did no reoccur with other subsequent antipsychotics.

The mechanism of risperidone induced oedema is not exactly known. Three mechanisms are described in literature for drug induced oedema, namely sodium overload, renal dysfunction, and hyperpermeability of blood vessels.[6] There are only a few reports about risperidone induced oedema in the literature and most of those cases occurred when risperidone was added to valproate[7,8] and the oedema was of angioneurotic type.[9,10] A mechanism related to suppression of C-1 esterase inhibitors has been reported to have a role in risperidone induced angio-oedema.[10] It is also suggested that oedema is unlikely to be secondary to any allergic reaction as IgE and complement levels were normal in the patient[11] while low complement levels have been reported in another case study.[9]

An alternative hypothesis for risperidone induced oedema may be atopy, ie. predisposition to develop localised immediate hypersensitivity reactions in parts of the body not in direct contact with the allergen. Atopy can cause urticaria, angio-oedema, allergic rhinitis and some forms of asthma. This aetiology is supported by a case report[9] that mentions similar reaction to lithium one year previously and family history of angio-oedema.

Conclusion

We conclude that periorbital, non tender, pitting oedema could be one of the unusual adverse effects of risperidone. The problem appears early during treatment and rapidly reverses with discontinuation of the drug. Whether the phenomenon has a predilection for the female gender with atopy still remains to be explored. As risperidone is one of the first line treatment choices in severe mental illness clinicians should be aware of the occurrence of this problem with the drug.

Declaration of interest: None.

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